EXHIBIT DX16

TO SECOND DECLARATION OF BENJAMIN W. HULSE IN SUPPORT OF DEFENDANTS' MOTION FOR RECONSIDERATION OF THE COURT'S DECEMBER 13, 2017 ORDER ON GENERAL CAUSATION

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Trials

STUDY PROTOCOL Open Access

Reducing Implant Infection in Orthopaedics (RIIiO): a pilot study for a randomised controlled trial comparing the influence of forced air versus resistive fabric warming technologies on postoperative infection rates following orthopaedic implant surgery in adults

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Abstract

Background: Approximately 70,000 to 75,000 proximal femoral fracture repairs take place in the UK each year. Hemiarthroplasty is the preferred treatment for adults aged over 60 years. Postoperative infection affects up to 3% of patients and is the single most common reason for early return to theatre. Ultraclean ventilation was introduced to help mitigate the risk of infection, but it may also contribute to inadvertent perioperative hypothermia, which itself is a risk for postoperative infection. To counter this, active intraoperative warming is used for all procedures that take 30 min or more. Forced air warming (FAW) and resistive fabric warming (RFW) are the two principal techniques used for this purpose; they are equally effective in prevention of inadvertent perioperative hypothermia, but it is not known which is associated with the lowest infection rates. Deep surgical site infection doubles operative costs, triples investigation costs and quadruples ward costs. The Reducing Implant Infection in Orthopaedics (RIIiO) study seeks to compare infection rates with FAW versus RFW after hemiarthroplasty for hip fracture. A cost-neutral intervention capable of reducing postoperative infection rates would likely lead to a change in practice, yield significant savings for the health economy, reduce overall exposure to antibiotics and improve outcomes following hip fracture in the elderly. The findings may be transferable to other orthopaedic implant procedures and to non-orthopaedic surgical specialties.

Methods: RIIiO is a parallel group, open label study randomising hip fracture patients over 60 years of age who are undergoing hemiarthroplasty to RFW or FAW. Participants are followed up for 3 months. Definitive deep surgical site infection within 90 days of surgery, the primary endpoint, is determined by a blinded endpoint committee.

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Discussion: Hemiarthroplasty carries a risk of deep surgical site infection of approximately 3%. In order to provide 90% power to demonstrate an absolute risk reduction of 1%, using a 5% significance level, a full trial would need to recruit approximately 8630 participants. A pilot study is being conducted in the first instance to demonstrate that recruitment and data management strategies are appropriate and robust before embarking on a large multi-centre trial.

Trial registration: ISRCTN, ISRCTN74612906. Registered on 27 February 2017.

Keywords: Surgical site infection, intraoperative hypothermia, forced air warming, resistive fabric warming, hemiarthroplasty

Background

Hip fracture is a common problem globally and a major cause of hospitalisation in the elderly. Approximately 70,000 to 75,000 proximal femoral fracture repairs take place in the UK each year, with the number continuing to rise with the ageing population. Effective treatment requires early surgery, most commonly with hemiarthroplasty. Postoperative infection remains one of the most serious complications of this procedure, affecting 2.5–3.5% of patients, and is the single most common reason for early return to theatre [1]. Additionally, length of hospitalisation is doubled, further surgery is often required and the cost of treatment is substantial [2]. Elderly patients who have to undergo re-operation are often left with impaired mobility and are unable to return to independent living. Furthermore, mortality after an infective complication is generally three times higher than that following uncomplicated surgery [3].

There are several factors that influence the risk of postoperative wound infection, including comorbidities, preoperative waiting time and the duration of surgery. Ultraclean ventilation in the operating theatre was introduced to limit the rates of infection. It is most commonly delivered through laminar flow canopies, which are now used in more than 60% of hospitals in the UK [4]. Nevertheless, a major drawback of laminar air flow ventilation [5] is that it makes the patient colder than conventional ventilation, with inadvertent perioperative hypothermia (IPH) being itself a known risk factor for infection. Following the demonstration that patient warming reduces the rate of surgical site infections (SSIs) in colorectal surgery [6], both the National Institute for Heath and Care Excellence (NICE) and the World Health Organization recommended maintenance of normothermia with active warming devices for all operations lasting longer than 30 min [7, 8].

Numerous intraoperative warming methods exist [9]. Forced air warming (FAW) – or convective air-warming transfer – has traditionally been considered the most effective non-invasive method of transferring heat to the patient, with systematic reviews conducted a decade apart showing that FAW is still the dominant technique in use [10, 11]. Resistive fabric warming (RFW), an air-free method of warming patients that works on a similar principle to an electric blanket, thus using conduction rather than convection, was included as an option for perioperative warming in recent NICE guidelines [12]. A systematic review of 67 randomised controlled studies from 1964 to October 2015 was not able to recommend one technique over the other for the prevention of IPH [11], yet their influence on postoperative infection rate is unknown.

Mobilisation of non-sterile air at floor level by FAW could potentially be compromising the sterility of the surgical site [13, 14]. Additionally, despite FAW filtration systems meeting HEPA standards, potentially pathogenic organisms have been found in hoses and blower systems [15–19]. Avidan et al. [16] found that higher airborne bacterial loads were associated with higher infection rates in patients kept warm with FAW, but this was not confirmed in later studies [13, 20, 21] and has been actively challenged by others [22–24]. Therefore, negating the protective effects of laminar airflow is highly disputed since the evidence does not directly link disruption of laminar airflow ventilation by FAW with risk of infection [25–29]. Until more is known about the potential influence of FAW on the incidence of SSIs, recent recommendations to not install laminar airflow in operating rooms for the purpose of preventing SSIs should not be implemented [30, 31].

Deep SSIs double operative costs, triple investigation costs and quadruple ward costs [2]. A cost-neutral intervention capable of reducing postoperative infection rates would likely lead to a change in practice, yield significant savings for the health economy and reduce overall exposure to antibiotics, as well as improve outcomes for hip fractures in the elderly. The RIIiO study compares infection rates with FAW or RFW after hemiarthroplasty for hip fracture. The findings may be transferable to other non-orthopaedic surgical specialties.

Methods/Design

Study hypothesis and objectives

We postulate that the risk of postoperative orthopaedic implant infection may be influenced by the choice of intraoperative warming technology used to

prevent IPH during hemiarthroplasty for hip fracture in elderly patients. RIIiO is a multicentre, parallel group, open label study randomising adults aged 60 years or over undergoing hemiarthroplasty following hip fracture to RFW or FAW. The primary endpoint is the observed event rate for definitive deep SSI within 90 days as determined by a blinded endpoint committee. A pilot study is being conducted in the first instance to inform the recruitment and data management strategies for the full trial. The pathway for participants is shown in Fig. 1 and summarised in the SPIRIT figure in Fig. 2 and SPIRIT checklist in Additional file 1.

Trial participants and informed consent

Potential participants are identified from admission records, theatre lists and from daily trauma meetings at six NHS hospitals in the UK. Determination of eligibility is based on a review of the case notes and a clinical assessment in relation to the inclusion and exclusion criteria. Patients with hip fracture are a surgical priority and will normally undergo surgery on the next available operating list. Such patients have a high incidence of comorbidities, will inevitably have suffered trauma and are likely to either be in pain or to have received opiate analgesia. In this emergency setting, it is inappropriate and not always possible to ask potential participants to review trial documentation. Given the number of factors influencing capacity or the ability to communicate an informed opinion, those patients who are listed for surgery on the next available operating list are not approached for consent prior to their surgery. Preoperative consent for randomisation is sought from an appropriate consultee in accordance with section 32, subsection 9b of the 2005 Mental Capacity Act in the UK. At the earliest opportunity after recovery from surgery, randomised participants are provided with the study information (Additional file 2) and written personal consent to continue in the pilot study is sought. For any participant who continues to lack capacity, postoperative written agreement from a personal consultee is sought. In all cases, consent is received by appropriately qualified and

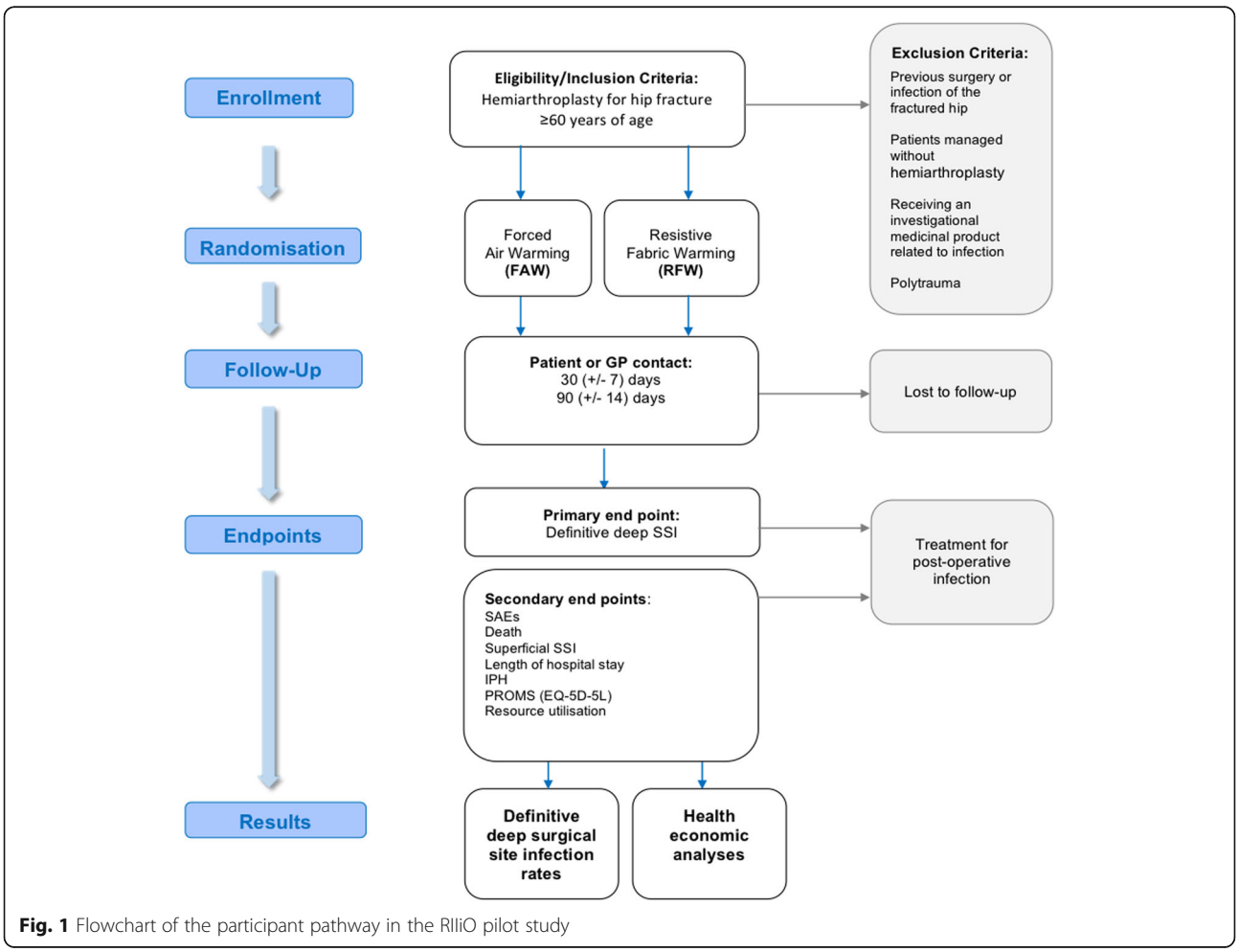

Fig. 1 Flowchart of the participant pathway in the RIIiO pilot study

	STUDY PERIOD					
	Enrolment	Allocation	Post-allocation			Close-out
TIMEPOINT	$-t_1$	0	t_1	t_2	t_3	t_x
ENROLMENT:						
Eligibility screen	X					
Informed consent	X					
Allocation		X				
INTERVENTIONS:						
Temperature monitoring		X				
ASSESSMENTS:						
Baseline assessments			X			
30-day follow-up assessments				X		
90-day follow-up assessments					X	

Fig. 2 SPIRIT figure for the RIIiO pilot study

Good Clinical Practice-trained research staff. Participants and their consultees are given the option to withdraw from the study at any time.

Inclusion and exclusion criteria

Participants must meet all of the following criteria:

(1) Provision of informed consent OR consultee declaration, (2) aged 60 years or over, (3) presenting with fracture of the hip and (4) scheduled to undergo hemiarthroplasty.

Patients may not enter the study if any of the following apply:

(1) Previous surgery or infection of the affected hip, (2) hip fractures related to polytrauma, (3) patients managed without hemiarthroplasty or (4) receiving an investigational medicinal product related to infection. Polytrauma is defined as 'multiple severe injuries involving three or more parts of the body'.

Randomisation

Prior to surgery, and after confirmation of a patient's eligibility, participants are allocated using simple randomisation, 1:1, in randomly permuted blocks of varying size without stratification by centre. Randomisation is through an established software package (MACRO) to either FAW or direct contact RFW. In the case of software failure, randomisation envelopes prepared in advance under the supervision of a qualified statistician are available to the local study team for immediate use in the emergency setting. The local research teams are responsible for randomisation and for informing the patient's general practitioner that they are participating in the study.

Study intervention

Only patients that undergo hemiarthroplasty can be recruited to this study. During their surgery, the participant is kept warm as part of their standard care using the technology to which they have been assigned. Both FAW and RFW are licenced and established techniques and are equally effective at preventing IPH [32–34]. Both warming devices are used in accordance with national guidelines as defined in NICE CG65. Temperature is measured just before the induction of anaesthesia, every 30 min during surgery, at the end of surgery and upon arrival in the recovery room. All thermometers are calibrated according to the standard protocol at each site. Whenever possible, temperature is measured with the automated 'SpotOn zfd' temperature monitoring system. IPH is defined as a temperature of less than 36 °C at the end of surgery or upon arrival in the recovery room. Where necessary for optimal clinical care, additional warming methods, such as actively warming intravenous fluids and blood products, may be employed at the discretion of the supervising clinician.

Baseline assessments

The following data are recorded at baseline, the majority being captured from routine clinical care records: (1) age, (2) sex, (3) estimated height and weight, (4) American Society of Anaesthesiologists physical status classification, (5) anatomical side affected, (6) date of admission, (7) date of surgery, (8) randomisation arm, (9) adherence to randomisation result, (10) duration of surgery, (11) use of ultra-clean ventilation in theatre, (12) cemented or uncemented prosthesis, (13) type of antibiotic-containing cement, (14) antimicrobial prophylaxis, (15) immuno-suppressants, (16) comorbidities (active malignancy, history of ischaemic heart disease, peripheral vascular disease, stroke, dementia, kidney disease/renal failure, diabetes mellitus, rheumatoid arthritis, systemic autoimmune disease and HIV), and (17) quality of life measures. Quality of life measures are obtained through the EQ-5D-5L questionnaire, which has been recommended for patients with hip fracture [35]. For those participants who lack capacity, the EQ-5D-5L questionnaire is completed by proxy through a consultee [36].

Subsequent assessments

Subsequent assessments are undertaken at 30 (± 7) days and 90 (± 14) days after surgery. In addition to recording EQ-5D-5L, the patients' medical records are consulted for any indication of deep or superficial SSI. Follow-up data include (1) date of discharge, (2) duration of hospital stay, (3) date[s] of readmission[s], (4) date of diagnosis of a potential deep SSI, (5) whether repeat surgery was performed, (6) radiological evidence of deep infection, (7) symptoms and signs indicative of a potential deep SSI (i.e. temperature, localised pain or tenderness, deep purulence from the wound or periprosthetic drain, spontaneous deep wound dehiscence), (8) results of deep tissue samples taken for histological analysis, (9) confirmed presence of microorganisms cultured from deep tissue/fluid samples (*Staphylococcus aureus*, coagulase-negative Staphylococcus sp., Streptococcus sp., Enterococcus sp., Pseudomonas sp. and/or other Gram negative organism[s]), (10) superficial SSI (i.e. involving only skin and subcutaneous tissues, purulent drainage from superficial incision, wound deliberately opened by the medical team due to pain or tenderness, erythema, localised swelling and/or warmth, positive aseptically obtained specimen from superficial incision or subcutaneous tissues (*S. aureus*, coagulase-negative Staphylococcus sp., Streptococcus sp., Enterococcus sp., Pseudomonas sp. and/or other Gram negative organism[s]), or (11) serious adverse events, including death (i.e. all-cause mortality).

Definitions of deep and superficial SSI

Deep and superficial SSI definitions are adapted from the Centres for Disease Control SSI criteria published in January 2016 [37]. Deep SSI is defined by the following criteria:

1) Infection arising within 90 days of the index surgery (where day 1 is the procedure date) AND
2) Involves deep tissues related to the incision (e.g. fascial and muscle layers, joint space or periprosthetic region) AND
3) At least one of the following:
   i. Purulent drainage from the deep incision or periprosthetic drain
   ii. A deep incision that spontaneously dehisces, or is deliberately opened or aspirated or biopsied by a surgeon, physician or other designee and an organism is identified by a culture- or non-culture-based microbiologic testing method performed for purposes of clinical diagnosis or treatment (e.g. not Active Surveillance Culture/Testing), or without a culture- or non-culture-based microbiologic testing method being performed
   iii. An abscess or other evidence of infection involving the deep incision or periprosthetic region that is detected on gross anatomical, histopathological exam or imaging test

Superficial SSI is defined by the following criteria:

a. Infection arising within 30 days of the index surgery (where day 1 is the procedure date) AND
b. Involves only skin or subcutaneous tissue related to the incision AND
c. At least one of the following:
   i. Purulent drainage from the superficial incision
   ii. Organisms identified from an aseptically obtained specimen from the superficial incision or subcutaneous tissue by a culture- or non-culture-based microbiologic testing method which is performed for purposes of clinical diagnosis or treatment (e.g. not Active Surveillance Culture/Testing (ASC/AST)
   iii. Superficial incision that is deliberately opened by a surgeon, physician or other designee and culture- or non-culture-based testing is not performed AND
   iv. The patient has at least one of the following signs or symptoms: pain or tenderness, localised swelling, erythema, heat
   v. Diagnosis of a superficial incisional SSI by a surgeon or physician

Endpoints and limitation of bias

The primary endpoint of the pilot study is the observed event rate for definitive deep SSI within 90 days of surgery. Secondary endpoints of the study are (1) superficial SSI, (2) IPH, (3) length of hospital stay, (4) EQ-5D-5L

measures, (5) resource utilisation and (6) serious adverse events, including death. Any post-randomisation readmission, clinic attendance or return to theatre with signs and symptoms at the site of surgery is considered a potential primary endpoint. Double blinding is not possible in this study. Any consequent risk of bias is limited by the use of a blinded endpoint committee (EPC) comprising clinicians with expertise in the diagnosis and management of bone and joint infection. For all potential deep SSIs, the EPC is provided with a summary of the participant's medical records relevant to the clinical episode redacted for personal identifiers and any information relating to their randomisation or intraoperative thermoregulation. The EPC confirms if a primary endpoint has been reached. Superficial SSIs are identified by the local care team.

The number of participants

Hemiarthroplasty carries a risk of deep SSI of approximately 2.5–3.5%. In order to provide 90% power to demonstrate an absolute risk reduction of 1%, using a 5% significance level, the full trial will need to recruit approximately 8630 participants over a 3-year period from a total of 30 sites (sample size calculations were performed in Stata, version 14SE [StataCorp, College Station, Texas]). The primary objective of the pilot study is to demonstrate that strategies for recruitment and data management for a trial of this size are appropriate and robust. Thus, there is no defined upper limit for the number of participants that can be recruited to the pilot study. Participants are recruited over a minimum period of 12 months at each site. To be able to keep the number of centres involved in the full trial to a maximum of 30, each pilot centre will be expected to recruit an average of two participants per week in the pilot study. The total number of patients recruited in the pilot study will be used to confirm the actual number of sites required for the full trial.

Trial management and safety reporting

The pilot study is co-ordinated by the Brighton and Sussex Clinical Trials Unit and a trial management group. A trial steering committee (TSC), comprising patient and public representatives, two independent clinicians and a statistician, makes recommendations to the trial management group regarding the conduct of the trial, recruitment and follow-up rates, and assesses the progression plan to the full trial based on extrapolation of data acquired in the pilot study. An independent Data Safety Monitoring Board (DSMB) evaluates patient safety and frequency of endpoints in an un-blinded analysis and makes recommendations to the TSC.

Discussion

A systematic review of 67 RCTs involving patient warming systems from 1964 to October 2015 could not identify whether FAW or RFW was more efficient at warming the patient [11]. To accurately study IPH and its consequences for orthopaedic patients, including postoperative infection rate, a standardised temperature monitoring protocol in a prospective trial with robust follow-up and adherence to CONSORT standards is needed [38]. An observational study in one hospital over a 2.5-year period suggested that the risk of developing deep infection up to 60 days after surgery was substantially greater for patients treated with FAW than RFW [14], but there were significant confounding factors in this study. The traditional assumption that FAW is the most effective non-invasive method of transferring heat to the body is based on warming comparisons that did not include RFW. Moreover, reduced infection rates with FAW have only been demonstrated, to date, with colorectal surgery [6], which is significantly different to orthopaedic trauma surgery. The RIIiO study will make substantial advances in the scientific understanding of whether or not the choice of patient warming technology influences the incidence of deep SSI. The pilot study will inform recruitment and data management strategies for such a trial.

Trial status

The RIIiO pilot study began recruiting on April 3, 2017, in Northumbria Healthcare NHS Foundation Trust and subsequently in Brighton and Sussex University Hospitals NHS Trust, Oxford University Hospitals NHS Foundation Trust, Milton Keynes University Hospital NHS Foundation Trust, Heart of England NHS Foundation Trust, Sheffield Teaching Hospitals NHS Foundation Trust and East Kent Hospitals University NHS Foundation Trust. Recruitment will cease in September 2018 and the pilot study will end in December 2018.

Additional files

Additional file 1: RIIiO pilot study SPIRIT checklist. (DOC 122 kb)

Additional file 2: RIIiO pilot generic PIS consent form. RIIiO pilot study generic patient information sheet and consent form: the information provided to patients and their consultees containing the form used to record their consent for enrolment in the trial. (PDF 529 kb)

Additional file 3: Full ethically approved RIIiO pilot study protocol. (PDF 1940 kb)

Abbreviations

EPC: Endpoint committee; FAW: forced air warming; GCP: good clinical practice; IPH: inadvertent perioperative hypothermia; NHS: National Health Service; NICE: National Institute for Health and Care Excellence; RFW: resistive fabric warming; SSI: surgical site infection; TSC/DSMB: Trial Steering Committee / Data Safety Monitoring Committee

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Paul, Fraser Old and Jennifer Bostock on the TSC. We are also grateful to Fraser Old for reviewing the participant documentation.

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Availability of data and materials

Not applicable. This manuscript does not contain any data.

Authors' contributions

The research question was identified by MS and the hypothesis developed with significant contributions from MR, CMH and MK, who collectively obtained the necessary funding to start the trial. MK and MS, assisted by NP, obtained ethical and Health Research Authority approval. MS, MK, NP, CMH and MR set-up the study operationally. SB provided statistical trial design expertise. MK prepared the initial draft of the manuscript. The views and opinions expressed in this publication are those of the authors and do not necessarily reflect those of 3M™, the Healthcare Infection Society, the Clinical Research Network, Wellcome Institutional Strategic Support Fund or Geratherm. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The pilot study is being conducted in full compliance with the principles of the Declaration of Helsinki and International Conference on Harmonisation Guidelines for Good Clinical Practice and has ethical approval from the West Midlands Coventry and Warwickshire Research Ethics Committee (REC ref. 16/WM/0451) and the Health Research Authority (HRA Ref 197521). The full ethically approved protocol is shown in Additional file 3. The study is sponsored by Brighton and Sussex University Hospitals NHS Trust.

Consent for publication

Not applicable. This manuscript does not contain data from any individual person.

Competing interests

MK, SB, NP and MS declare that they have no competing interests. CMH declares that he has been loaned equipment by various companies and paid honoraria by 3M and Molnlycke Health Care. MR declares that he has received speaker fees from Heraeus and research funding from Heraeus, 3M, Zimmer and Convatec.

Publisher's Note

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EXHIBIT DX17

TO SECOND DECLARATION OF BENJAMIN W. HULSE IN SUPPORT OF DEFENDANTS' MOTION FOR RECONSIDERATION OF THE COURT'S DECEMBER 13, 2017 ORDER ON GENERAL CAUSATION

UNITED STATES DISTRICT COURT
DISTRICT OF MINNESOTA

In re: Bair Hugger Forced Air Warming Products Liability Litigation

MDL No. 2666 (JNE/DLS)

This Document Relates to:

Nancy Axline v. 3M Co., et. al.
17-cv-00511

EXPERT REPORT OF WILLIAM R. JARVIS, M.D.

I. INTRODUCTION

This specific causation expert report concerns the perisprosthetic joint infection (PJI) suffered by Ms. Nancy Axline ("Ms. Axline"). I hereby reincorporate, in its entirety, my expert report previously provided with respect to general causation, including citations and exhibits, as if fully stated here. I also reincorporate my deposition testimony and opinions previously provided with respect to general causation.

In addition to the documents I reviewed previously for my general causation expert report, I also have reviewed the medical records of Ms. Axline cited in Exhibit A, the deposition transcripts of Drs. Wenzel, Mont, Holford, and Borak, and the supplement to the report of Said Elghobashi, Ph.D. concerning the Bair Hugger model 505. I also have reviewed the deposition transcripts of Dr. Adolph Lombardi, Dr. Nestor Narcelles, Sarah Wynn, PA-C, Ms. Axline, and Mr. Ronald Axline. In addition, there may be documents produced by Defendants and/or third parties in this matter that may impact my opinions as well. I therefore reserve the right to amend and/or supplement this report upon receipt and review of additional information obtained through such discovery.

II. BRIEF MEDICAL HISTORY OF MS. AXLINE

Based on my careful review of the records in this case, and my experience as a medical doctor and a clinician, it is my opinion to a reasonable degree of medical certainty that Ms. Axline was an appropriate candidate for her left total hip arthroplasty (THA) surgery and that the pre-operative skin preparation,surgical

antimicrobial prophylaxis, and incision care that were employed throughout the surgery complied with the standard of care.

In April 2009, Ms. Axline was a 52-year-old woman with a history of hypothyroidism, gastroesophageal reflux disease (GERD), hypertension, osteoarthritis of both hips, depression, anxiety, anemia, and dyslipidemia. She stood 5 feet 5 inches tall and weighed 198 pounds, giving her a body mass index [BMI] of 32.9. She did not have a history of past or present smoking or present alcohol use. Shehad undergone a THA procedure on her right side on February 7, 2008.

By way of background, on May 2, 2007, Ms. Axline attended a consultation with Dr. Lombardi at Joint Implant Surgeons, Inc. for evaluation of both of her hips. Ms. Axline reported she had bilateral leg pain for the past 4-5 years. There was 2+ pitting edema noted of her left lower extremity. She was observed to have a moderate limp. Her left leg was shorter than her right leg by ½ cm. X-rays of the right hip demonstrated moderate to severe joint space narrowing, bone densing, and osteophyte and cyst formation. X-rays of the left hip demonstrated mild joint space narrowing, bone densing, and osteophyteand cyst formation. She was instructed to continue conservative therapy.

Ms. Axline followed-up with Dr. Lombardi at Joint Implant Surgeons, Inc. on January 17, 2008. She reported increased pain in the right hip. X-rays of the right hip demonstrated severe joint space narrowing, bone densing, and osteophyte and cyst formation. It was noted since the last appointment her progress had deteriorated. Surgery was recommended to consist of a total right THA.

On February 7, 2008,Ms. Axlineunderwent a right THA, performed by Dr. Lombardi, at Mount Carmel Hospital. She tolerated the procedure without complications. Post-operative x-rays showed the right hip prosthesis in satisfactory position. While in the hospital she worked with physical therapy and was able to reach her goals before discharge. Ms. Axline was able to be discharged home in stable condition on February 8, 2008. No home health or outpatient therapy was needed at this point.

Ms. Axline followed-up at Joint Implant Surgeons, Inc. and saw Jeff Williams, PA-C on March 20, 2008. Her right hip incision was well healed, without signs and symptoms of infection. Ms. Axline was using a cane for ambulation, and a slight limp was observable. X-rays of the right hip revealed the right THA was in satisfactory position and alignment. She was instructed to follow-up in 12 months.

On September 19, 2008, Ms. Axline saw Dr. Lombardi, at Joint Implant Surgeons Inc. for evaluation of her left hip. She wanted to discuss scheduling of her left THA. She reported her pain was becoming severe, and she was ready to proceed with the procedure. The surgery was scheduled for January 15, 2009. At her pre-

operative physical on December 23, 2008, her laboratory results revealed her iron was low. She saw Dr. Husain, her private physician, at Harding Memorial Healthcare on December 30, 2008 and was referred to Dr. Matura for evaluation of her anemia.

Ms. Axline then underwent anEsophagogastroduodenoscopy (EGD) and colonoscopy on January 9, 2009. These were performed by Dr. Maturu at Ohio Marion Area Physicians. Her EGD showed antral gastritis and she was started on omeprazole. Her colonoscopy revealed mild diverticulosis. A small bowel X-ray series was ordered to rule-out any mass lesions in the small bowel causing her to have blood loss. This was completed on January 12, 2009, and showed normal progression through to the colon.

On February 12, 2009 Ms. Axline had an appointment with Dr. Husain at Harding Memorial Healthcare. She was using a cane for ambulation at that time and was positive for tenderness to the left hip. She was given a prescription for Percocet to help with her pain until surgery could be scheduled.

Ms. Axline was cleared to proceed with surgery on April 1, 2009 by Dr. Bloch at Mount Carmel Hospital. She was 52 years old at the time.The THA was performed on April 21, 2009 at Mount Carmel Hospital, by Dr. Lombardi.At the time of this surgery, her American Society of Anesthesiologists (ASA) score was 3. Her skin antiseptic was Chloraprep and she was given Ancef prophylactic antibiotic (2 grams) 30 minutes before her incision. She received general and spinal anesthesia and was intubated. Her surgical time was 126 minutes (2 hours and 6 minutes). An upper body Bair Hugger set to 43°C was used during the procedure. Her intraoperative temperatures were all 35.8°C, except for one temperature at 35.7°C. Dr. Lombardi wore a sterile personal isolator suit and double gloved during the entire procedure. If lights were moved, this was done by the circulator and new sterile handles were used for each case. A pressure monitoring device monitors the air pressure in the operating room at all times. The Bovie was used approximately 2 minutes during the entire procedure. One scalpel was used for the initial incision and then a new scalpel is used for the rest of the procedure. No blood transfusions were given during the procedure. Post-operative X-rays revealed satisfactory left hip replacement. She tolerated the procedure well.Post-operatively she did have some pruritus, related to the Duramorph dressing. Pain control was initially an issue, but was sufficiently controlled before discharge. There also were concerns for a possible early ileus, but this was ruled-out with an X-ray of her abdomen. Throughout hospitalization,Ms. Axline worked with physical therapy and was able to meet her short term goals. Upon discharge, it was recommended that she have home health or outpatient physical therapy for continued rehab. Ms. Axlinewas discharged to home with her husband on April 24, 2009.

Ms. Axline followed-up with Jeff Williams, PA-C at Joint Implant Surgeons Inc. on May 20, 2009. Ms. Axline's chief complaint was left hip pain. It was noted she had no previous history of infection in the left hip. The left hip incision was documented to be well healed. X-rays of her left hip revealed the left THA was in satisfactory position and alignment. She was instructed to continue post-operative restrictions and to follow-up with Dr. Lombardi in two weeks. She also was instructed to not bear any weight on the left lower extremity and to use a walker.

On June 12, 2009,Ms. Axline saw Dr. Lombardi at Joint Implant Surgeons Inc. She continued to complain of left hip pain and difficult ambulation. She reported the pain as severe and constant. The left hip incision was again documented as well healed. There was mild erythema noted at the site. A moderate limp was observable with ambulation. Ms. Axline was instructed to return to the clinic in three weeks, and if her symptoms continued then review for possible revision would be needed. A prescription for Percocet 5/325 was given to her to help control her pain.

Ms. Axline continued to have left hip pain and again followed-up with Jeff Williams, PA-C on July 2, 2009, for evaluation. X-rays of the left hip did not show any changes. Ms. Axline's white blood count (WBC) was 7,300 cells/mm^3, erythrocyte sedimentation rate (ESR) was 55 (normal: 0-30), and her C-reactive protein (CRP) was 55 (normal 0-9). A WBC scan revealed 2+ uptake in the L hip "predominantly in the trochanter region". Suspecting a possible infection, an aspiration of her left hip was scheduled for July 24, 2009. This was completed and was negative (no fluid was aspirated). On August 3, 2009, a repeat WBC was 8,600, ESR 69 and CRP 73.7. Because of the rising WBC, ESR and CRP and a positive WBC scan, another left hip aspiration was performed on August 4, 2009. This aspirate showed a WBC of 80,812 cells/mm^3, 91% polymorphonuclear cells and grew out methicillin-susceptible *Staphylococcus aureus*(MSSA). The MSSA was susceptible Ciprofloxacin, Clindamycin, Erythromycin, Gentamicin, Nitrofuratoin, Oxacillin, Tetracycline, Trimethoprim-Sulfamethoxazole, Vancomycin, Levofloxacin, Daptomycin, Linezolid and Rifampin. It was resistant to Penicillin. Subsequently, Dr. Lombardi reviewed these recordsand recommended that Ms. Axline have a left hip radical debridement to treat her MSSA surgical site infection (SSI). Dr. Lombardi noted in his deposition that "there was no evidence at any time of an incisional infection.

On August 21, 2009, Dr. Lombardi performed drainage, debridement, removal of prosthesis and placement of prostalac, which is a 9x125 mm Biomet cement spacer mold using Cobalt cement with 3 grams of vancomycin and 3.6 grams of tobramycin per unitto her infected left THA. There is no mention of any discharge or pus at the incision or anterior to the fascia. The femoral component and canal were debrided. Ms. Axline tolerated the procedure well. During the hospitalization, on August 22, 2009, Dr. James Smith frominfectious diseases was consulted to assist in the management of her intravenous (IV) antibiotics. She did have complaints of calf tenderness, but a Duplex Ultrasound ruled out any abnormalities. Ms. Axlinealso

was seen by physical therapy during her hospitalization. A PICC line was placed on August 24, 2009 for continued IV antibiotic therapy (i.e., Ancef 2 grams q 8 h). She was determined to be stable for discharge on August 25, 2009. Home health services were arranged through Marion General Hospital for continuation of her IV antibiotic therapy.

On September 18, 2009 Ms. Axline was seen at Mount Carmel Hospital by Derrick Johnson, MD at the request of Dr. Lombardi for medical clearance before her left hip re-implantation. She was cleared for surgery. This same day, she followed up with Dr. Lombardi at Joint Implant Surgeons Inc. At this point, she continued on IV antibiotic therapy (Ancef). Her staples were removed this visit without complications. Re-implantation of her left hip was scheduled for October 5, 2009.

Ms. Axlineunderwent the second of the two-stage revision surgeries on October 5, 2009 at Mount Carmel Hospital by Dr. Lombardi. At the time of this surgery, her American Society of Anesthesiologists (ASA) score was 2. Again, she had Chloraprep antisepsis and received Ancef (2 grams) and gentamicin (80 mg) surgical antibiotic prophylaxis approximately 21-57 minutes before her incision. She tolerated the procedure well and there were no complications. Post-operative x-rays revealed normal alignment status post THA revision on the left. Intra-operative cultures were negative. Her peripherally inserted central catheter (PICC) line was replaced during the hospitalization. She was again consulted by infectious disease, it was determined at that point to continue her on IV Ancef for a short time and if her wounds healed nicely, she would be switched to Keflex. Ms. Axline also required 1 unit of packed red blood cells due to her hemoglobin being low before discharge. Ms. Axlineworked with therapy and met her goals with assistance of her husband for all transfers. She was determined to be stable for discharge on October 7, 2009. Home health services were again arranged through Marion General Hospital.

On October 27, 2009,Ms. Axline followed-up with Jeff Williams, PA-C at Joint Implant Surgeons Inc. Her staples were removed without complications. She was instructed to do toe touch weight bearing until follow-up in three weeks. She had this follow-up on November 18, 2009. Her incision site on her left hip was documented to be well-healed. X-rays of the left hip revealed her THA in satisfactory position and alignment. Her diagnosis were osteoarthritis of the left hip status post THA on the left, failed THA due to infection/inflammation of prosthesis of the left hip, and status post left hip radical debridement with left hip re-implantation. Ms. Axline was instructed to continue post-operative restrictions. She was released to return to work on December 21, 2009. Ms. Axline was to continue 25% weight bearing for one week, 50% for one week, 75% for one week, and then 100%.

Ms. Axline returned to Joint Implant Surgeons Inc. and saw Jason Hurst, M.D. on March 20, 2012 for her annual exam. She reported she had recently had multiple falls, which had aggravated her left hip symptoms. A slight limp was ob-

served with ambulation. X-rays of the bilateral hips showed satisfactory position and alignment. Outpatient therapy was recommended. She also underwent an evaluation of her right shoulder on this date. Ms. Axline reported she had had right shoulder pain for years, but it has progressively worsened. An X-ray of right shoulder demonstrated mild, joint space narrowing, bone densing, and osteophyte formation. She was diagnosed with osteoarthritis of her right shoulder. She was administered a Kenalog intra-articular injection to her right shoulder. She was instructed to follow-up in 6 months.

It is my opinion to a reasonable degree of medical certainty that the standard of care was employed throughout the above surgeries and hospital stays.

In follow-up visits from October 2009 through 2012, Ms. Axline presented well with negative x-rays and only occasional pain (1-2/10 on pain scale). The index left THA infection was diagnosed and treated properly, and ultimately was successfully resolved.

Conclusion and Synopsis of Key Opinions

All the opinions I express in this report are opinions I hold to a reasonable degree of scientific and medical certainty.

On April 21, 2009, Ms. Axline underwent a left THA procedure (i.e., index procedure). Her pre-operative skin preparation (i.e., Chloroprep) and prophylactic antimicrobial agent, dose, and timing (i.e., 2 grams of Ancef administered 30 minutes before incision) were consistent with applicable guideline recommendations and followed appropriate standards of medical practice at all times. The duration of the initial implant surgery was 78 minutes. Regional spinal anesthesia without endotracheal intubation was given. The estimated blood loss was 175 ml and no blood transfusions were given. The nursing operating room records indicate: "No break in sterile technique; No apparent cross –contamination; Aseptic technique maintained; Copious wound irrigation implemented; Implementedimplant protocol; Minimal handling of implant prior to placement". I am unaware of any reports of contaminated surgical tools or supplies, nor any deviations from standard surgical practice or infection control procedures. Based on my review of available records, the medical care comported with all accepted standards of medical and surgical practice.

Despite the appropriate care provided by the medical care professionals, approximately 3weeks after the left THA (May 20, 2009), Ms. Axline returned to Dr. Lombardi complaining of pain, at this and subsequent evaluations (i.e., June 12, 2009, July 2, 2009, and July 24, 2009). no incisional infection was noted. On July 2, 2009, an elevated ESR and CRP were detected. On July 7, 2009, an abnormal WBC scan—with 2+ uptake in the femoral trochanter region--was found. Subsequently (on August 3, 2009), the WBC, ESR and CRP continued to rise and on August 4,

2009an aspirate of the left hip revealed elevated WBCs, mostly polmorphonuclear cells, and the culture grew MSSA. Despite noting on July 31, 2009 that "left hip incision is well healed", a deep MSSA-SSI was suspected and documented at the August 21, 2009 left THA revision surgery, when the prosthesis was removed and an antibiotic spacer was inserted and Ms. Axline began a 6 week course of IV antibiotic therapy. At the time of this prosthetic joint infection (PJI), there was no documentation of any incisional or pre-fascia SSI (i.e., superficial or incisional SSI).Thus, four months after the index procedure, Ms. Axline was diagnosed with a MSSA-PJI which necessitated an incision and drainage (I&D), a two-stage revision surgery including removal of herleft THA prosthesis, and placement of an antibiotic spacer followed by six weeks of antimicrobial therapy with agents targeting MSSA. After the infection cleared, a permanent hip prosthesis was re-implanted (October 5, 2009). The findings of an elevated ESR and CRP, abnormal WBC scan, positive left hip aspirate culture for MSSA, and evidence of PJI at the time of the I&D surgery, along with Ms. Axline's response to antimicrobial therapy, are all consistent with a nosocomial intra-operatively acquired MSSA-PJI.

III. METHODOLOGY

Medical care providers routinely use a causation assessment that courts refer to as a "differential diagnosis" or "differential etiology" in assessing the cause of a patient's medical condition. Regardless of its name, this methodology requires "ruling in" all potential causes of the condition and then "ruling out" unlikely causes of the condition. In the Bair Hugger litigation, the proper, generally accepted methodology requires ruling in all potential causes of the bacteria inoculating the joint and then ruling out unlikely causes of the bacteria that inoculated the joint based on the facts and evidence in each case. As to biological plausibility, bacteria are the actual ***causes*** of the PJI; that is, the only biological causes of infection are bacteria that have inoculated the joint during exposure at the time of surgery. The determinative issue is the most likely ***mechanistic source*** of the bacteria that inoculated the joint.

Using the foregoing method to identify potential causes for Ms. Axline's MSSA-PJI, the medical literature confirms that the majority of PJIs are caused by pathogens that are deposited in the surgical incision during the surgery.[1] Put simply, without microbial pathogens and dissemination to the deep joint space, ***no patient*** would suffer a PJI regardless of how many risk factors he or she may possess or his or her susceptibility to infection.[2] While it is true that Ms. Axline—like nearly all

[1] *See* Jarvis General Causation Expert Rpt. at 4–8, 16 (collecting scientific sources).
[2] As discussed during my deposition, these "risk factors" do not ***cause*** PJI, but rather may increase the likelihood that PJI ***will develop*** if bacterial contamination of the

patients—had several risk factors for potential infection, including obesity, it is my clinical and professional medical opinion that none of these conditions impacted her development of PJI.

Based on my review of the medical records in this case, my differential diagnosis/etiology confirms that the care rendered to Ms. Axline, the practices of the surgical team, the operating room conditions and environment, and other applicable factors, together with the medical literature concerning forced air warming technology and Bair Hugger warming specifically, and the mechanistic Computational Fluid Dynamics (CFD) study performed by Dr. Elghobashi, the most likely source of Ms. Axline's MSSA-PJI was the inoculation of her surgical wound at the time of her index surgery on April 21, 2009.

Knowing the overwhelming majority of PJIs are caused by bacteria deposited during surgery, I turn to the potential sources of pathogens inside the operating room. Relevant medical literature confirms that the vast majority of bacteria, often measured as CFUs, in the operating room come from the surgical team.[3]

A. Rule In / Rule Out: Potential Causes of Bacteria Contaminating the Joint

1. Bair Hugger

The Bair Hugger significantly increases the quantity of particles and bacteria over the sterile surgical field resulting in a significantly increased risk of PJIs as previously outlined in my general causation expert report and deposition. *It is my expert opinion to a reasonable degree of medical certainty that when a Bair Hugger blanket is used during orthopedic arthroplasty surgeries, it substantially increases the risk of a PJI.*

The following points support my opinion that the Bair Hugger significantly increases risk of PJIs:

- As outlined in my expert report on general causation, a thorough review of the peer-reviewed medical literature, including the elevated

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prosthesis/joint/incision occurs. Indeed, offending pathogens or colony forming units (CFUs) of the organism must not only exist, but such pathogens must deposit at the surgical site in the prosthesis/deep joint space in order for a PJI to occur at the time of surgery.

[3] *See* Jarvis General Causation Expert Rpt. at 5 (citing, *e.g.*, Whyte 1988) *see also id.*at 21 (noting patient-specific interventions that reduce likelihood of patient as cause).

odds-ratio reported in the McGovern study, together with various case reports.

- The expert CFD report prepared by Dr. Said Elghobashi regarding the Bair Hugger 750,[4] along with his supplemental report regarding the impact of the Bair Hugger 505, on the operating room unidirectional airflow. According to Dr. Elghobashi's study and the videos generated as part of that study, the Bair Hugger causes significant disruption of operating room airflow, leading to increased number of skin squames over and in the sterile field.

- As further detailed in my general causation report, the Bair Hugger has two mechanisms for contaminating the operative field with bacteria—through blowing non-filtered, non-sterile air and through releasing excess heat that disrupts operating room airflow. Each mechanism causes increased squames and therefore bacteria over the sterile field.

2. Heating Ventilation and Air Conditioning (HVAC) System

Based on my experience and conducting outbreak investigations for the Centers for Disease Control and Prevention (CDC), the HVAC of the operating room is a potential source of airborne contamination. Based on the limited documents received from Mount Carmel East Hospital, the operating room used by Dr. Lombardi in performing Ms. Axline's THA was the same as designed in 2003. It used a unidirectional airflow system with a two-filter system. Records do not show that the HVAC system was impaired or contaminated. Thus, the properly-functioning HVAC system could not have increased Ms. Axline's risk of developing a PJI. It is my professional opinion that it did not increase the risk.

3. Surgical Team Contamination

The surgical team, if not properly scrubbed in, may contaminate the sterile field and increase the risk of infection, including increasing the risk for PJI during THA. Records do not show that the surgical team failed to follow the appropriate aseptic procedures and sterile techniques. The surgical personnel in the operative field all wore sterile single use personal isolator suits with their own air supply. Absent evidence to the contrary, the surgical team complied with appropriate

[4] This work has since been published in an internationally renowned, peer-reviewed journal. He X, Karra S, Pakseresht P, Apte SV, Elghobashi S. *Effect of heated-air blanket on the dispersion of squames in an operating room.* INT J NUMER METHOD BIOMED ENG. 2018;34:e2960

standards of care, rendering the likelihood of the surgical team's contaminating the wound very small. It is my professional expert opinion that the surgical team did nothing to increase the risk of infection during Ms. Axline'ssurgery and that her infection was not the result of any action or inaction by this team.

4. Patient's Flora

One of the potential sources of bacteria is the patient's flora at or immediately adjacent to the surgical incision. However, there is a general consensus that PJIs are caused by airborne contamination and by direct contact by the patient's own flora.[5] The use of Chloroprep (i.e., 2% chlorhexidine and 70% isopropyl alcoholas skin preparation would nearly eliminate skin flora at the surgical incision site and therefore the likelihood of the PJI being caused by the patient's own flora around the surgical site is very unlikely. Ms. Axline's own flora can thus be ruled out. Such skin flora is more commonly associated with superficial or incisional SSIs, which Ms. Axline did not have.

5. Surgical Procedure and Technique

Based on my review of the medical records, it is evident that the surgeons and staff followed appropriate standards of care and proper surgical procedure and technique. Dr. Lombardi testified that he practices sterile technique, including during Ms. Axline's surgery.[6]There is no evidence that at any time of the procedure there was a break in the sterile field by any procedure or technique documented in the medical records. Without the deposition testimony of the surgical team and staff, there is no evidence that anything occurred outside what is mentioned in the medical records or Dr. Lombardi's or Dr. Narcellas' depositions. There was no evidence of any contamination of the surgical instruments or iatrogenic contamination of the sterile field. Based on the records reviewed, it is my opinion held to a reasonable degree of medical certainty that the surgical procedure and technique was within the standard of care and that likelihood of the surgical procedure or technique of the surgical team causing bacteria to inoculate the joint is very low. The surgical procedure and technique can therefore be ruled out as a likely cause.

6. Other Potential Causes

Based on the medical records, literature, and previously disclosed opinions of Defendants' experts, I have compiled the list above regarding potential causes of

[5] *See, e.g.*, PROCEEDINGS OF THE INTERNATIONAL CONSENSUS MEETING ON PERI-PROSTHETIC JOINT INFECTION (2013) at 115–16 ("[T]he focus of our recommendation is to reduce the volume of bacteria in the operating room with particular attention to airborne particles.").

[6] Lombardi Dep. 93:24-94:2.

bacteria reaching the sterile field. There is no peer-reviewed published literature to support that cabinets, lights, tables, computers, or narcotics increase the risk of PJI. I reserve the right to supplement this section and report if any new information should arise from the depositions of fact witnesses or other discovery regarding this matter.

7. Possible Causes Not Ruled In

In light of my review of Defendants' expert reports on general causation, and the depositions of Drs. Wenzel and Mont, I have considered the following possible causes identified by Dr. Mont and have not ruled them in as plausible sources that can cause bacteria to inoculate the joint or other areas of the sterile field: anesthesia machines; surgical lights; computer monitors; computer consoles; electrocautery devices; bovie; surgical drapes; cabinets along the walls; the suction drain; sterilized surgical equipment; drop buckets; trash receptacles; or surgeons moving their hands.[7] Based on my review of the literature, my training, education, and experience, I agree with Defendants' expert Dr. Wenzel that there is no evidence in the scientific community indicating that any of the foregoing variables increase the likelihood of bacteria inoculating the joint.[8]

Further, in light of my review of the deposition of Dr. Lombardi, I agree there is no evidence that Ms. Axline had a superficial incisional wound infection,[9] or any other type of ongoing infection that could have caused the PJI,[10] and that there is no evidence her PJI was caused by the trash bin in the operating room,[11] the Bovie machine,[12] chairs in the operating room,[13] or the cabinets in the operating room.[14] Dr. Lombardi agreed there is no evidence that the tools, implant, gowns, drapes, or anything else used during Ms. Axline's surgery was contaminated.[15] Dr. Lombardi testified there is no evidence that his gloves were perforated at any time during Ms. Axline's surgery.[16] Dr. Lombardi testified that one of the purposes of the laminar screen in the operating room where Ms. Axline's surgery took place was to

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[7] *See, e.g.*, Mont General Causation Expert Rpt. at 10–11.
[8] *See, e.g.*, Wenzel Dep. at 99:4-104:2.
[9] *See, e.g.*, Lombardi Dep.At 90:11-20.
[10] Lombardi Dep. 94:16-23. Also no evidence that Ms. Axline had any infection, including a urinary tract infection Lombardi Dep. 94:24-95:3, or any dental work that would cause an infection. Lombardi Dep. 95:4-9.
[11] Lombardi Dep.At 92:12-16.
[12] Id. at 92:17-19.
[13] Id. at 92:20-21.
[14] Id. at 92:23-93:2.
[15] Dep. 95:9-15.
[16] Lombardi Dep. 93:14-20.

minimize the airborne contamination over the sterile field.[17] Dr. Lombardi testified if the sterile field was contaminated during Ms. Axline's surgery, it would have been noted either by himself or a member of his team in Ms. Axline's medical record,[18] and that there is no evidence that the sterile field was in any way contaminated or compromised during Ms. Axline's primary left hip surgery.[19] Additionally, I agree with Dr. Lombardi that post-operative SSIs, like the one Ms. Axline was diagnosed with, are believed to occur via bacterial inoculation at the time of surgery or as a result of bacterial contamination of the wound via open pathways to the deep tissues layers.[20]

B. Bair Hugger is the Most Likely Cause of Bacteria Inoculating the Joint

1. Methodology using Relative Risk and Differential Etiology

Differential diagnosis and/or etiology often use epidemiological studies and relative risk ratios to determine causation in a specific case. As discussed below, numerous studies, including the McGovern study, indicate directly and indirectly that the Bair Hugger more than doubles the risk of PJI. A relative risk ratio of 2.0 in and of itself shows that the device or drug at issue is the most likely cause of the disease. Thus, I agree with Defendants' expert Dr. Holford that a relative risk ratio >2.0 indicates that a device or drug is the most likely cause of the disease.[21] Thus, absent any deviation from the standard of care by the physicians, staff, or hospital, the Bair Hugger is the most likely cause of a patient's PJI in an orthopedic arthroplasty surgery.

In the case of Ms. Axline, I have analyzed all other plausible causes of a PJI in surgery and have used her medical records to rule out those variables as the most likely cause of her implant being inoculated with bacteria causing her PJI. The McGovern study and/or Dr. Elghobashi's CFD model paired with the Stocks and Darouiche studies each independently confirm that the Bair Hugger is the most likely cause of Ms. Axline'sPJI.

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[17] Lombardi Dep. 89:13-17.
[18] Lombardi Dep. 93:3-13.
[19] Lombardi Dep. 93:9-13.
[20] Lombardi Dep. 87:19-88:7.
[21] At his deposition, Dr. Holford agreed that "[i]f the incidence of disease in an exposed group is more than twice the incidence in the unexposed group, the probability that exposure to the agent in a similarly situated individual is also greater than 50%." *See* Holford Dep. at 225:19-226:1. The Reference Manual states as much. *See, e.g.*, REFERENCE MANUAL ON SCIENTIFIC EVIDENCE, 3d ed. at 612 (Federal Judicial Center).

2. Quantifying the Risk Posed by Bair Hugger

CFD Model and Peer-Reviewed Literature

The results of Dr. Elghobashi's CFD test makes clear that the Bair Hugger causes significant turbulence in the operating room, particularly around the operating room table. As a result of that disruption, the Bair Hugger significantly increases the number of skin squames reaching the surgical site, the operating room table, and side tables where instruments, fluids, and implants are located. Indeed, the Bair Hugger increases the density of particles large enough to carry bacterial CFUs by more than 10 CFU/m^3 in a very short time: less than a minute after the Bair Hugger reaches the appropriate temperature for warming patients.

The International Consensus of Orthopedic Surgeons (ICOS), along with a large body of medical literature, confirms that the probability of PJI correlates directly with the quantity of bacteria that reaches the surgical wound during an orthopedic arthroplasty procedure. The literature also demonstrates that use of the Bair Hugger increases particles over the sterile field. The overwhelming number of particles in the operating room are from the surgical staff and patient. A range of at least 1 million to as much as 900 million skin squames are shed, per hour, by surgical staff during a typical procedure. As confirmed by Dr. Wenzel, many of these particles carry bacteria.[22]

As discussed in my general causation report, the Stocks and Darouiche studies correlate particles and CFU over the surgical site. Stocks et al. correlated the number of CFUs with the number of 10 micron particles, while Darouiche et al. correlated the number of CFUs with the incidence of PJI in orthopedic procedures. Based on the empirical data collected in the Darouiche study, the authors ultimately concluded that for every increase of 10 CFUs/m^3 there was a doubling of the risk of PJI.[23]

Given Dr. Elghobashi's CFD test, along with the results of the Stocks and Darouiche studies, use of the Bair Hugger during the surgery of Ms. Axlineis the most likely cause of the bacteria inoculating the joint and thus the cause of PJI in this case.

The McGovern Study

As previously stated in my general causation expert report, the McGovern study reports a relative risk ratio (odd ratio) of 3.8 comparing use of Bair Hugger to conductive blankets in arthroplasty surgeries. However, relying on a draft data set,

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[22] *See* Wenzel Dep. at 50:16–21 ("Forty percent of particles can carry bacteria.").
[23] *See* Jarvis General Causation Expert Report at 24 (citing Stocks and Darouiche).

Defendants' experts assert that the odds ratio is 2.8 rather than 3.8. Whether one uses the published data in the McGovern study or the draft data used by Dr. Holford, the evidence shows more than a doubling of the risk (RR of ≥ 2.0) when the Bair Hugger forced air warmer is used compared to non-forced air warming devices such as conductive blankets. The risk ratio reported by McGovern et al. further shows that Bair Hugger is the most likely cause of bacteria inoculating the implant.[24] Under normal operating room and surgical procedures, the most likely cause of Ms. Axline'sPJI was thus the Bair Hugger.

IV. CONCLUSION

In summary, I have conducted a careful and thorough medical record review allowing me to provide the Court with a causation assessment and/or differential diagnosis and/or differential etiology for Ms. Axline's PJI. As part of my methodology and process in this case, I have ruled out all other potential causes of infection and determined that the Bair Hugger is the most likely cause of Ms. Axline's PJI. In doing so, I have considered all medical evidence made available to me, as outlined herein, and also have reviewed all countervailing possibilities that might be postulated based on Ms. Axline's pre-existing medical conditions as well as the conditions and practices prevailing at the hospital and operating room at the time of herleft hip index surgery.

Using this careful, deliberative, well-accepted methodology, comparing Ms. Axline'smedical history to other infection cases I have seen over my career, and based on my review of all of the medical and scientific papers addressing these issues, as well as my own scientific training, knowledge, and clinical experience, I conclude to a reasonable degree of scientific and medical certainty that Ms. Axlinedeveloped anMSSA-PJI after herleft THA procedure on April 21, 2009, and that MSSA was inoculated into her operative wound directly or indirectly by the Bair Hugger.

Moreover, based on the available medical records and literature, CFD testing, including Dr. Elghobashi's peer reviewed publication and the videos he generated as part of his large-eddy simulation (LES) CFD study, the expert report of Dr. Samet, the 3.8 odds-ratio reported in the McGovern study and by Dr. Samet, which can be used to demonstrate specific causation, the deposition testimony of Dr. Holford, and other available data discussed in this report and my general causation report, it is my opinion within a reasonable degree of medical certainty that use of the Bair Hugger in Ms. Axline's index surgery was the most likely cause of the bacterial exposure that contaminated herleft hip prosthesis in this case.

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[24] *See, e.g.*,Holford Dep. at 225:19-226:1.

Dated: August 13, 2018

William R. Jarvis, M.D.

William R. Jarvis, M.D.

Appendix A

1. Depositions of Dr. Narcelles, Dr. Lombardi, Mrs. Axline, Mr. Ronald Axline, and Sarah Wynn, PA-C.

2. Selected medical records of Mrs. Axline:

a. Consent form for left total hip arthroplasty (THA) on 4-21-2009.

b. Operative report for left THA on 4-21-2009.

c. Anesthesia report for left THA on 4-21-2009.

d. Nursing pre-admission record for left THA on 4-21-2009.

e. Nursing intra-operative record for left THA on 4-21-2009.

f. Consent for left THA revision 10-5-09.

g. Anesthesia pre-operative evaluation for left THA on 10-5-09.

h. Anesthesia record for 10-5-09 left total hip arthorplasty (THA).

i. Nursing intraoperative record forleftl THA revision on 10-5-2009.

i. Post-operative flow sheet for left THA on 10-5-2009,.

j. Infectious disease medical records from 8-22-09 to 11-24-09.

k. Joint Implant Surgery, Inc. medical records.

l. Medical records for Mt. Carmel New Albany Surgical Center (February 7, 2008 through October 7, 2009.

3. Scholten R, et al. The incidence of mild hypothermia after total knee or hip arthroplasty: A study of 2600 patients. J of Orthopedics 2018;15:408-11.

4. Medical chronology of Mrs. Nancy Axline from 1/30/2002 through 4/17/2017.

EXHIBIT DX18

TO SECOND DECLARATION OF BENJAMIN W. HULSE IN SUPPORT OF DEFENDANTS' MOTION FOR RECONSIDERATION OF THE COURT'S DECEMBER 13, 2017 ORDER ON GENERAL CAUSATION

UNITED STATES DISTRICT COURT

DISTRICT OF MINNESOTA

Louis Gareis and Lillian Gareis, Plaintiff, v. 3M Company and Arizant Healthcare, Inc., Defendant.	**VOLUME X** File No. 16-CV-4187 (JNE/FLN) May 29, 2018 Minneapolis, Minnesota Courtroom 12W 9:07 a.m.

BEFORE THE HONORABLE JOAN N. ERICKSEN
UNITED STATES DISTRICT COURT JUDGE

(JURY TRIAL - VOLUME X)

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Q. So in that video, there was no ventilation in the room?
A. Correct.
Q. Okay. So I take it you didn't mean to suggest that that video was similar to a positive pressure operating room with unidirectional airflow that we're discussing here today?
A. No. I do think it's similar. I mean what that video clearly showed is that when someone opens the door and walks into a room, they create tremendous air movement and disturbances, and those disturbances extended, I think we saw, about 90 percent of the way across the room.

Insofar as neither CFD calculations in this case had opening doors, I mean, we both ignored opening doors, and they are major. They have a major effect, and so I do think this is relevant to the current case.

Q. Do you agree that CFD is a reliable method to model airflow?
A. Yes.
Q. And particle flow?
A. Yes.
Q. And heat transfer?
A. Yes.
Q. And temperature changes can affect airflow, correct?
A. I agree.
Q. Turbulence can affect airflow, correct?

EXHIBIT DX19

TO SECOND DECLARATION OF BENJAMIN W. HULSE IN SUPPORT OF DEFENDANTS' MOTION FOR RECONSIDERATION OF THE COURT'S DECEMBER 13, 2017 ORDER ON GENERAL CAUSATION

UNITED STATES DISTRICT COURT

DISTRICT OF MINNESOTA

In Re: Bair Hugger Forced Air Warming Devices Products Liability Litigation	File No. 15-MD-2666 (JNE/FLN)
	October 24, 2017
	Minneapolis, Minnesota
	Courtroom 12W
	9:04 a.m.

BEFORE THE HONORABLE JOAN N. ERICKSEN
UNITED STATES DISTRICT COURT JUDGE

THE HONORABLE FRANKLIN L. NOEL
UNITED STATES MAGISTRATE JUDGE

THE HONORABLE WILLIAM H. LEARY
RAMSEY COUNTY DISTRICT COURT JUDGE

(MOTIONS HEARING)

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constriction. That's what the *Glastetter* court in fact said in quotes. And so the plaintiffs may feel that they don't have to meet the burden set forth in *Glastetter*, but the Eighth Circuit didn't say that.

THE COURT: Thank you.

MR. BLACKWELL: So, Your Honor, getting back to the type of evidence that the plaintiffs have here, I was talking about biological plausibility as sort of an interim sort of a screening, because not even biological plausibility gets you across the hurdle into proper scientific valid proof of causation, and many courts have so held in causation cases such as this, but the plaintiffs don't even have that.

So what they're relying on are these tertiary secondary endpoint exploratory studies, studies that involve bubbles and particles and had the beginnings of smoke studies and studies that expressly disclaim causation, and they don't even demonstrate, as I said, biological plausibility. So what are they relying on here? They're relying on those what I call smoke particle -- well, bubble and particle studies. They also rely on animation, a CFD. And no court we could ever found --- could ever find this computation of fluid dynamics animation. We never found a court that's found that a computer animation, especially an unvalidated one, is a substitute for even showing biological

plausibility, much less causation in the real world.

They rely on the McGovern study, and we're going to dive deep into McGovern, Your Honors, because at no matter what level you look at the McGovern, on the surface it is -- it is flawed on the surface. It's flawed for the reasons that Your Honors have already acknowledged that it has many confounders that were not were controlled for and never even considered, but as we plunge the depths of it, we hope to share, and my colleague Cory Gordon who spent quite a bit of time in the UK digging this out will come up to talk about how that McGovern data is in fact cooked, it's manipulated data, it's flawed data, it was manipulated when the data went from Dr. McGovern and got into the hands of Dr. Scott Augustine and his consort, and they essentially manipulated the numbers to try and influence statistical significance, and we can show that to Your Honors as an additional reason why the McGovern study is hopelessly flawed.

In the context of McGovern, we also want to talk to Your Honors about the Augustine 2017 study. This is a study that the plaintiffs were for until they were against it, and they were for it and volunteered it, Dr. Samet, their expert, at his deposition as additional reliance material. Sorry, Judge Noel.

MAGISTRATE JUDGE NOEL: I have this feeling of

they have that shows an impact in the real world. Our view is that those opinions are based upon completely unreliable data to the extent they premised in McGovern, to the extent premised in the exploratory studies, CFD, studies about particles, air movement, etc., those exploratory studies are completely insufficient proof to bridge the analytical gap between -- around the science plaintiffs have and the science they're required to put on to meet the Rule 702 requirements.

As I mentioned in the opening, Your Honors, for the McGovern specific aspect of this I'll ask my partner Corey Gordon to speak to just McGovern because that is -- he developed McGovern. I want to speak to the general state of the science and the fact that the plaintiffs' view and theory of the science is generally rejected in the scientific and medical community.

I wanted to take a couple things out of order, just to set the table a little bit, because there was a lot said again about this SSI versus PGI issue, and I want to pull up a slide that might be the Rosetta Stone that kind of gets to the bottom of this, if I could pull up number 37. And what this is, is international consensus meeting, as Your Honors can see, and that of the prosthetic joint infection, and so this is an international consensus meeting that is about PJI.

going to pull this all up at once just to show which things fall under which. The plaintiffs have particles, bubbles, and CFD, that's way on the left, for experiment also slash theoretical. Biological plausibility are studies that actually test whether the Bair Hugger is releasing bacteria in the OR or increasing the quantity of bacteria in the OR. There's not that. And epi, there's various types of epidemiology studies. And simple argument is they don't have to have epidemiology, it is not really -- shouldn't be tantamount to an argument they don't have to have anything or that we could simply have particles and bubbles.

And obviously we talked about gold standard, gold standard types of epidemiology and clinical trials before, but the point here is that the plaintiffs are relying on the particles and the bubble studies and the litigation CFD created in litigation, and they're relying on McGovern. And McGovern, we will take a deep dive on that, but McGovern disclaims a causal basis for any positive association. They don't have epidemiology, they don't have any biological plausibility studies, they don't have any gold standard proof of causation, and so that leaves us talking about particles and bubbles, et cetera.

And so that's where we are. I wanted to tee this up because there may be other arguments that Your Honors hear where we'll we point out which box we're talking in at

UNITED STATES DISTRICT COURT

DISTRICT OF MINNESOTA

In Re: Bair Hugger Forced Air Warming Devices Products Liability Litigation	File No. 15-MD-2666 (JNE/FLN)
	October 26, 2017
	Minneapolis, Minnesota
	Courtroom 12W
	9:39 a.m.

BEFORE THE HONORABLE JOAN N. ERICKSEN
UNITED STATES DISTRICT COURT JUDGE

THE HONORABLE FRANKLIN L. NOEL
UNITED STATES MAGISTRATE JUDGE

THE HONORABLE WILLIAM H. LEARY
RAMSEY COUNTY DISTRICT COURT JUDGE

(MOTIONS HEARING - VOLUME III)

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of is this going to be useful in any of the cases, the 4,000-plus cases that we have in the MDL and the 60-plus that we've got in Ramsey County? And Dr. Elgobashi has got a temperature input that we have strong reason to believe that's not the temperature that you'd find if you measured under the draping in any operating room in America. And so the relevance of this to any of the cases, the bellwethers, and so forth that may be tried is dubious.

But even beyond that, the plaintiffs don't cite any case where a CFD has been admitted as proof of causation of a medical injury. Dr. Elgobashi himself doesn't give the opinion that general causation can be premised on a CFD. No other expert in this case has given the opinion that general causation conclusion can be based solely on a CFD. And the plaintiffs haven't pointed to any study, and we haven't found one that says that a CFD can be used to prove the cause of an infection.

And in the plaintiffs' summary judgment opposition, again, all they say is it's mechanistic evidence. They don't claim that it can get them over the hurdle of general causation.

Another thing that the plaintiffs' medical experts rely on is an inference. An inference that increase in particulate matter in the operating room means you have an increase in bacteria. So if the Bair Hugger increases